The beta adrenergic theory of the atopic abnormality in bronchial asthma

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In 1931, one of the founding fathers of American allergy research, Francis M. Rackemann, wrote the following lines: "The situation is somewhat analogous to that of a loaded gun. A good deal of knowledge is being obtained about the great variety of triggers (extrinsic and intrinsic causes) which fire the charge; but why is the gun loaded? And what constitutes this load?"[1]

These questions refer to the fact that only a minority of the total population shows some form of atopic hypersensitivity despite that, by and large, identical conditions of antigenic exposure must be presumed to exist for all members of the same population.[2, 3] The nature of the atopic abnormality in bronchial asthma (or in any other manifestation of atopic allergy), which determines that only a relatively confined segment of a given population shows asthmatic reactivity, i.e., is affected pathologically, is as yet unexplained, but it has been traditionally approached through immunological concepts.

These concepts derive from an association of a physiochemically and biologically distinct antibody, the reagin, with this disorder, and the production and unusual reactivity of this type of antibody is thought to account for the atopic abnormality in asthma.[4] However, as has been extensively discussed,[5] immunological concepts cannot easily account for some of the significant facts surrounding this disease.

Therefore, based on model experiments and other considerations, an alternative to the classical concept, which came to be known as the beta adrenergic

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theory of bronchial asthma, has been postulated and presented by this author in early 1962,[6] and on subsequent occasions.[7-10] Basic scientific and clinical investigations relative to this theory have not progressed sufficiently to establish its validity. Nevertheless, the rapidly growing interest in our approach and the inescapable confusion which accompanies any new theoretical development make it my eminent responsibility to present this first comprehensive account of the theory which has been advanced.

SCOPE AND APPROACH

This paper proposes to concern itself with the developmental background of the beta adrenergic theory, what the theory states, the presently available supportive evidence, and how it may explain the most consistently characteristic features of this disease.

An understanding of these principal aspects of the theory requires prior knowledge of some recent advancements in the biochemistry of adrenergic action in the physiopharmacology of infection, as well as additional information usually outside the sphere of interest of allergists or immunologists. Therefore, an attempt will be made to review and organize this information into a pattern which is expected to meaningfully serve the purpose of this article.

In the ensuing discussion, no attempt will be made to consider separately the two clinically recognized types of bronchial asthma, i.e., the "extrinsic" and "intrinsic" types, since both appear to share essentially the same physiopathological features. In fact, bronchial asthma will be regarded not as a "syndrome" but as a "disease" which, regardless of the potentially differing nature of the triggering event in any given case, has only one common underlying pathogenesis. Furthermore, we shall proceed on the traditional assumption that bronchial asthma belongs in the class of the so-called "immediate type" hypersensitivities, i.e., in a group of conditions in which the clinically manifested response is mediated by immunologically released and pharmacologically active agents.

THE PHARMACOLOGICAL MEDIATORS OF ANTIGEN-ANTIBODY RESPONSES

The pharmacological mediators which are currently considered to be involved in immediate type hypersensitivities can be arbitrarily separated into two groups: (1) three small chemically defined compounds: histamine, serotonin, and acetylcholine, and (2) a group of larger compounds, the so-called slow-reacting substances and plasma kinins.[11]

In addition, the catecholamines (epinephrine, etc.) may be considered a third group of mediators of the allergic response. Their inclusion is justified since each of the first group and most of the plasma kinins release, or are capable of releasing, the catechols.[12-17] Thus, the latter are at least potential participants in the allergic reaction. Although in this capacity, in contrast to the other mediators, they usually have no untoward effect, under certain conditions their entry into the reaction may be harmful.[5, 18] In many tissues of most species the catecholamines are the principal natural antagonists of the first two groups of mediators and thus play a major role in determining the nature of ultimate

reactivity of the target cells to these immunologically or otherwise released substances.[5]

There is much disagreement regarding the relative importance of any one of the above mentioned pharmacologic mediators in immediate type hypersensitivities in general, and in bronchial asthma in particular. Opinions differ even further on the question of what other potentially important active substances are involved in any of the immediate type hypersensitivities.[11] Nonetheless, whatever the relative importance of any one of the established or suspected mediators may be, for our purpose here the important point is that the catecholamines are to be considered among the pharmacologic mediators of the allergic response.

THE CATECHOLAMINES

The term "catecholamine" refers generically to all compounds containing a catechol nucleus (a benzene ring with 2 adjacent hydroxy groups, i.e., dihydroxybenzene which is also known as "catechol") and an amine group (Fig. 1). To date, 4 catecholamines have been positively identified in mammals: epinephrine, norepinephrine, dopamine, and N-methyl epinephrine.[5] Isopropylnorepinephrine (the "natural" isoproterenol?) was also said to be detectable in adrenal medullary cells[19] and to be released on stimulation of bronchial nerves.[20] It is now believed that this substance is not isopropylnorepinephrine but an undefined active metabolite of norepinephrine.[21]

Two such compounds, epinephrine and norepinephrine, are synthesized as well as secreted by mammalian cells and have important functions in neuroendocrine integration, the first primarily as a hormone and the second as a neurotransmitter at both peripheral and central levels.[5]

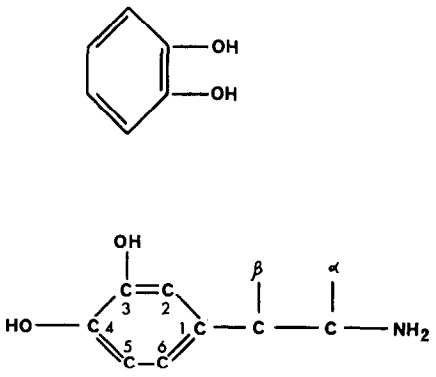

Fig. 1

The upper part of the figure shows the catechol nucleus. Below that the basic structure of catecholamines, consisting of a catechol nucleus and a side chain, can be seen. The structure permits substitutions to be made on the aromatic ring and the alpha- and beta-carbon atoms, as well as the terminal amino group, to yield a great variety of compounds with adrenergic activity.

THE RECEPTOR AS THE PHARMACOLOGICALLY SPECIFIC TARGET-CELL COMPONENT OF CATECHOLAMINE ACTION

Following release or exogenous administration, the catecholamines elicit their characteristic effect through the activation of certain cells which are their specific targets and can, therefore, be called "target cells." A target cell can be further defined as one which is endowed with a receptive substance (a "receptor") possessing a site with a steric configuration complementary to the amine. Due to its natural affinity, the released or administered amine combines with the complementary receptor site, thereby initiating a chain of biochemical reactions of largely undetermined nature culminating in the observable adrenergic end-response. Thus, activation of the target cell requires a primary combination between amine and receptor, and therefore it is the receptor which should be regarded as the pharmacologically specific component of the target cell.

Since none of the adrenergic receptors have been conclusively identified so far, it is difficult to select adequate descriptive terms for them. Conventionally, therefore, they are designated either by the effector response resulting from their activation, by the relative potencies of different sympathomimetic amines acting on a variety of effectors, or by their specific blocking agents.

On this basis, there appear to be 2 principal types of adrenergic receptors, termed alpha and beta.[22] The adrenergic functions currently associated with each of these receptors are listed on Table I. At present, this classification seems to leave many areas of adrenergic activity unexplored, and there are adrenergic responses which cannot be easily integrated into these 2 categories.[23-25] Nevertheless, the dualistic receptor classification of Ahlquist has been, and continues to be, an extremely useful approximation of adrenergic action.

The alpha adrenergic receptors can be blocked by various representatives of the ergot alkaloids, haloalkylamines (i.e., Dibenamine, phenoxybenzamine), benzodioxans, and imidazolines, etc. The beta adrenergic receptors can be blocked by dichloroisoproterenol (DCI), pronethalol (nethalide, Alderlin), propranolol (Inderal), MJ-1999, (4-[2-isopropylamino-1-hydroxyethyl] methane sulfonanilide hydrochloride), MJ-1998 (4-[2-methylamino-1-hydroxypropyl] methane sulfonanilide hydrochloride), and others. Among the catecholamines, norepinephrine acts mainly on alpha receptors, isoproterenol acts almost exclusively on beta receptors, while epinephrine possesses dualistic action.

ADENYL CYCLASE AS THE BETA ADRENERGIC RECEPTOR

Although the adrenergic receptors have had these names for many years we are only just beginning to get acquainted with their fundamental nature, at least as far as the beta receptor is concerned. Important advances have been made with chemical,[26, 27] biochemical,[28-31] and electrophysiological methods,[32, 33] and from these combined approaches a general picture of the beta receptor is emerging which implies that it is an enzyme, the so-called adenyl cyclase.

Adenyl cyclase is present in all animal cells examined to date, with the exception of nonnucleated erythrocytes.[30] It has been localized to the cell membrane in 2 types of cells, i.e., in avian erythrocytes and rat liver cells.[34, 35] However, this location of the enzyme may not necessarily be on or in the mem-

Table I. *Functions associated with each of the adrenergic receptors*

	Alpha receptor	*Beta receptor*
Lung		
	Bronchial contraction	Bronchial relaxation
Blood vessels		
	Vasoconstriction (skin and mucosa, abdominal viscera,* cerebral, pulmonary, renal, salivary glands)	Vasodilatation (skeletal muscle, liver*)
Heart		
		Cardioacceleration (S-A node) augmentation of atrial contractility and conduction velocity
	Myocardial ectopic excitation (cyclopropane anesthesia)	Augmentation of ventricular contractility, conduction velocity, automaticity, and rate of idiopathic pace-makers
Eye		
	Iris-dilator contraction (mydriasis), nictitating-membrane contraction	Ciliary muscle relaxation (for far vision)
Stomach		
	Contraction of sphincters	Decrease in motility and tone
Intestine		
	Decrease in motility and tone, contraction of sphincters	Decrease in motility and tone
Urinary bladder		
	Contraction (Trigone and sphincter)	Relaxation (Detrusor)
Others		
	Myometrial contraction† (rabbit, dog, human, etc.), pilomotor contraction, localized "adrenergic sweating," splenic capsule contraction, production of thick, viscous secretion by salivary glands, hepatic glycogenolysis (?)	Myometrial relaxation† (rat, nonpregnant cat, human, etc.) Eosinopenia
		Muscle glycogenolysis, inhibition of peripheral glucose uptake,
	Free fatty acid mobilization (?)	free fatty acid mobilization (?)

*Following physiologic concentrations of epinephrine, vasodilation predominates in skeletal muscle and liver, and vasoconstriction in other abdominal viscera.

†Response depends on amount of circulating estrogen and progesterone, and other factors.

brane per se, but it is perhaps a component of a specialized organelle related to the membrane (i.e., in rabbit skeletal muscle cells).[36] Concerning its chemical nature, indications are that it may be a lipoprotein.[37] Such cellular location and chemical nature, as well as the fact that its activation appears to be the earliest chemical manifestation of adrenergic action, are all in harmony with the classical concepts of receptors. Likewise, its activation by catecholamines parallels the characteristic order of potency which has been found to apply to the activation

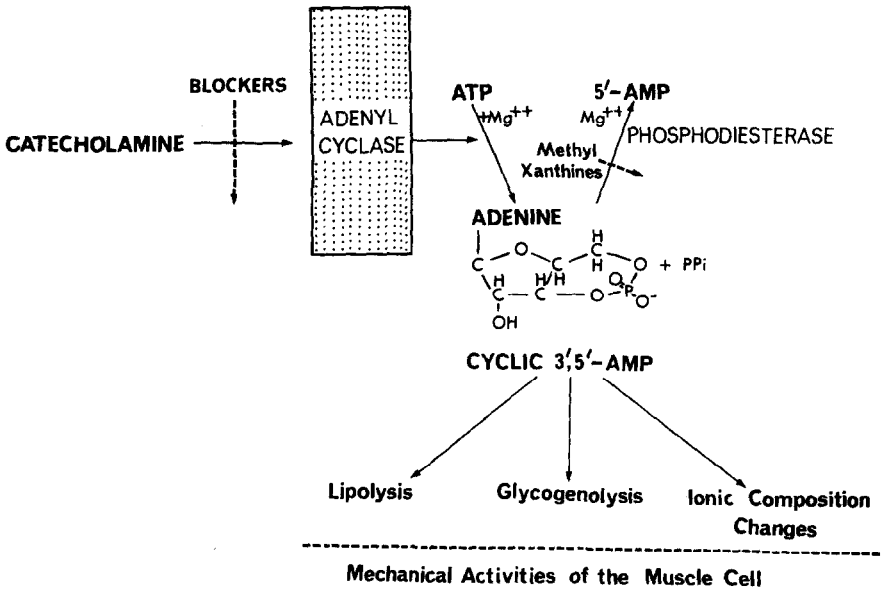

Fig. 2
Schematic representation of the biochemical pharmacology of adrenergic action.

of the hypothetical beta receptor. Thus, isoproterenol is considerably more potent than epinephrine in activating adenyl cyclase, while epinephrine is more effective than norepinephrine.[38]

In the presence of magnesium ions, the adrenergically activated adenyl cyclase catalyzes the formation of a cyclic nucleotide (and inorganic pyrophosphate) from adenosine triphosphate (Fig. 2). This cyclic nucleotide, adenosine-3′,5′-phosphate (cyclic 3′,5′-AMP), is a mononucleotide of adenylic acid with the phosphate group diesterified at carbons 3′ and 5′ of the ribose moiety. Cyclic 3′,5′-AMP is destroyed by a phosphodiesterase, specific for mononucleotide 3′,5′-bonds, which converts it to 5′-AMP.

Thus, the catecholamine-adenyl cyclase interaction results in the formation of cyclic 3′,5′-AMP, which then functions as an intracellular mediator of catecholamine action by modifying enzyme activities and permeability barriers. In this regard, glycogenolysis and lipolysis are the 2 areas of catecholamine activity in which the mediating role of cyclic 3′,5′-AMP has been studied in detail. It has been established that cyclic 3′,5′-AMP converts inactive phosphorylase to active phosphorylase, which in turn causes the breakdown of glycogen to glucose-6-phosphate.[28] In the liver, glucose-6-phosphatase converts the latter substance to glucose which is then released into the extracellular space. Glucose-6-phosphatase is not present in the muscle cell, and glucose-6-phosphate is anaerobically metabolized to lactic acid causing an increase in blood lactate level. Nevertheless, as in the liver, cyclic 3′,5′-AMP induces glycogenolysis also in the muscle with the resultant intracellular accumulation of glucose-6-phosphate and noncompetitive inhibition of glucose phosphorylation. Since phosphorylation is required for the entry of glucose from the extracellular to the

intracellular space, the rate of entry of glucose into muscle will be reduced. Thus, hyperglycemia following epinephrine is the result of 2 simultaneously occurring adrenergic effects: (1) hepatic glycogenolysis resulting in the release of glucose, and (2) muscle (and other extrahepatic) glycogenolysis resulting in the inhibition of the peripheral uptake of excess glucose. In addition to phosphorylase, cyclic 3′,5′-AMP also activates a specific lipase in adipose tissue which then causes lipolysis of triglycerides. Release of free fatty acids from adipose tissue then increases the blood level of fatty acids.[39, 40]

THE RELATIONSHIP BETWEEN THE BIOCHEMICAL AND MECHANICAL EFFECTS OF CATECHOLAMINES

The previously mentioned effects of catecholamines on the carbohydrate chemistry of muscle cells, which form the greater portion of adrenergically innervated cells, have led to attempts to relate these effects to changes in the mechanical reactivity of the adrenergic target cells.

This field of investigation apparently finds itself in the same difficult position as do other areas of biological research which attempt to deal with the links between the chemical reactions which provide energy and the functional apparatus which directs its use. Indeed, several biochemical mechanisms have been proposed to explain the mechanical (contracting or relaxing) effects of catecholamines on muscle cells,[32, 33, 41] but none of these theories has yet been experimentally established as a satisfactory interpretation of the biochemical mediation of adrenergically induced muscular activity.

Most recent evidence strongly indicates, however, that relaxation of uterine smooth muscle to catecholamines is in fact mediated by the adenyl cyclase-3′,5′-AMP system.[42] For the purpose of this paper, the significance of this finding is that smooth muscle relaxation following epinephrine does in fact appear to be linked with a chain of biochemical events initiated by the activation of adenyl cyclase, accumulation of 3′,5′-AMP, and subsequent glycogenolysis.

THE TWO EXPERIMENTAL MODELS FOR THE INVESTIGATION OF THE NATURE OF THE ATOPIC ABNORMALITY IN BRONCHIAL ASTHMA

An examination of how these biochemical and pharmacologic advancements may influence our thinking on asthma will have to revolve around the already mentioned key problem of this disease, which is the elusive nature of the atopic abnormality. Historically, the interpretation of the symptomatology and the underlying reaction sequence of asthma was patterned after those of the anaphylactic guinea pig.[43] True enough, like most of the immediate group of hypersensitivities, including anaphylaxis, many of the manifestations of asthma are mediated by immunologically released and pharmacologically active substances. However, in anaphylaxis we appear to be dealing with a normal antibody response to an unnatural exposure to antigen, whereas in asthma an abnormal antibody response to natural antigenic exposure is believed to be involved.[44] Anaphylactic reactivity of the sensitized guinea pig depends on the immunologic release of an amount of pharmacological mediator sufficient to be toxic for every member of the same species. In contrast, asthmatic persons possess an abnormal

reactivity to otherwise nontoxic concentrations of endogenously released or exogenously administered pharmacologic mediators (for details see Szentivanyi and Fishel[5]).

Another essential difference is the major contributory role played by respiratory infection in asthma, whereas infection has not been shown to be causally related to anaphylaxis, the Arthus reaction, or serum sickness. The latter conditions are produced artificially, but asthma cannot be induced at will. Conversely, asthma can be precipitated by a number of unrelated stimuli, whereas anaphylaxis of sensitized guinea pig can be brought about only by the specific antigen.

Therefore, experimental anaphylaxis cannot be used as a laboratory model for the investigation of the nature of the atopic abnormality in bronchial asthma. On the other hand, it was felt that no significant progress could be expected in the elucidation of this abnormality unless there is at our disposal a meaningful, artificially producible, and controllable laboratory model in which such abnormal mechanisms can be investigated.

In searching for a model we were led by the premise that, if it is to be meaningful, the model must be able to imitate not only the immunologic but also the pharmacologic abnormality of the asthmatic state. The latter is manifested against substances which, in mammalian physiology, serve as the natural chemical organizers of autonomic action. It seemed likely, therefore, that an altered reactivity to these agents could be most effectively produced through some alteration of normal autonomic regulation significant enough to result in an autonomic imbalance.

The first model: The hypothalamically "imbalanced" anaphylactic guinea pig

With Prof. G. Filipp, our first attempts to establish a more meaningful experimental counterpart of the atopic state were made in the years of 1952 to 1958 by studying hypothalamically "imbalanced" anaphylactic guinea pigs.[45-49, 51-55] The rationale behind this approach was as follows:

There are 2 reciprocally antagonistic divisions in the hypothalamus: the anterior hypothalamus, which mediates mainly parasympathetic responses, and the posterior hypothalamus, the stimulation of which results chiefly in sympathetic responses. Because of this arrangement, the hypothalamus appears to be a central level of autonomic organization which still permits a fair degree of separation between parasympathetic and sympathetic representations. A functional balance between these antagonistic divisions is thought to be important in maintaining normal autonomic functions.

By electrolytic removal of one division or electric stimulation of the antagonistic division, it was possible to profoundly alter the anaphylactic reactivity of guinea pigs both immunologically and pharmacologically. Similar experiences have been reported later by Gellhorn,[55] Korneva and Khai,[56] and Luparello and associates.[57] Thus, both from the immunologic and pharmacologic standpoints, the conditions so produced more closely approximated those of the human atopic state than anaphylaxis does. Nevertheless, it was felt that the artificial state of such a surgically induced hypothalamic imbalance is far removed from that natural setting (involving various inherited and/or acquired factors) which

may surround the development of an asthmatic state. In order to imitate more closely those naturally occurring conditions, some of which, i.e., infection, may conceivably serve as a developmental background for asthma, it was felt that the *Bordetella pertussis*-induced hypersensitive state may serve as a more appropriate model.

The second model: The *Bordetella pertussis*-induced hypersensitive state of mice and rats

Injection of living or killed *Bordetella pertussis* organisms into certain strains of mice and rats modifies the normal responses of these animals to a number of various stimuli.

With Prof. C. W. Fishel and Prof. D. W. Talmage, a systematic analysis of these altered responses was started at the University of Colorado School of Medicine in 1961, and it is still being intensely pursued. The possible applicability of the results of these investigations to bronchial asthma is implied by the following principal features of the *B. pertussis*-induced altered responsiveness:

1. Hypersensitivity to endogenously released or exogenously administered histamine, serotonin, bradykinin,[58-60] and at least in one strain, to acetylcholine.[61]

2. Hypersensitivity to less specific stimuli such as cold, changes in atmospheric pressure, respiratory irritants, etc.[63-65]

3. In sharp contrast with the aforementioned increased sensitivities, a reduced sensitivity to catecholamines and, concerning some metabolic parameters, a reversal of normal adrenergic activity.[14, 62, 76-83]

4. Enhanced antibody formation in general (adjuvant activity), and facilitated production in quantity of antibodies not ordinarily induced by antigenic stimulation. These antibodies exhibit many of the features peculiar to atopic reagin and are thought to represent its animal counterpart.[66-74]

5. Presence of a marked eosinophilia.[75]

The critical advance in our experiments, paving the way for a meaningful analogy to bronchial asthma, has been the finding that the hypersensitivity of the pertussis-sensitized mouse to pharmacological mediators may be due to an acquired imbalance of the 2 adrenergic effector systems, i.e., to a reduced functioning of the beta receptors or of some of the reactions between receptor activation and adrenergic end-response. In particular, the deprivation of the normal beta adrenergic inhibition of peripheral (extrahepatic) uptake of glucose appears to be instrumental in the production of the hypersensitivity to the various pharmacological mediators. In addition, this increased rate of entry of glucose may well be the biochemical explanation for the pertussis-induced alterations of the immune response.[5, 14, 18, 76-83]

THE PRINCIPAL TENETS OF THE BETA ADRENERGIC THEORY

Based on the above experiments and other considerations, the beta adrenergic theory regards asthma not as an "immunological disease" but as a unique pattern of bronchial hyperreactivity to a broad spectrum of immunological, psychic, infectious, chemical, and physical stimuli. This view gives to the anti-

gen-antibody interaction the same role as that of a broad category of nonspecific stimuli which function only to trigger the same defective homeostatic mechanism in the various specialized cells of bronchial tissue.

Activation of the same defective mechanism by such a broad spectrum of unrelated triggers is believed to be made possible by the unusual character of the class of allergic mediators as a biologically distinct category of natural substances. This refers to the fact that the pharmacological mediators of antigen-antibody responses, when viewed from the standpoint of their probable physiologic function, are among those substances which are thought to be the natural chemical organizers of autonomic action, that is, of homeostatic control.[5, 11] Consequently, regardless of the immunological or nonimmunological nature of the triggering event, mainly the same mediators would be expected to be involved.

Homeostatic adjustment to these influences requires, among others, mobilization of the adrenergic neurotransmitters (catecholamines) and their balanced (uninhibited) interaction with the 2 major adrenergic effector systems. The theory postulates that the atopic abnormality in asthma lies in the reduced functioning of one of these 2 antagonistic systems, the beta adrenergic system, irrespective of what the triggering event may clinically be in a particular case (immunological, infectious, psychic, etc.). In this situation, the adrenergic neurotransmitters are released in the face of a relatively unavailable beta effector system, and the resultant adrenergic imbalance deprives the bronchial tissue from its normal counter-regulatory adjustment.

The most critical component of this malfunctioning effector system, the beta adrenergic receptor, is currently being identified with an enzyme, the adenyl cyclase. It follows, therefore, that the fundamental abnormality common to all asthmatic persons may be an inherited or acquired enzyme deficiency, that is, a relative unavailability of the enzyme because of its reduced synthesis, partial blockade, or production of defective enzyme molecules incapable of binding the adrenergic neurotransmitter.

Progression of the disease process from a subclinical to a clinical form conceivably requires the operation of a preparatory and a triggering factor. At first, the enzymatic abnormality must be extensive enough to set the stage for the development of a functional imbalance. This might occur, for instance, with massive saturation of the receptor-binding sites in the course of a chronic subclinical upper respiratory infection. Secondly, there may be a triggering event powerful enough to result in an extensive and prolonged increase in the rate of firing of adrenergic neurons or in the massive release of catecholamines from extraneuronal stores. Such an event would conceivably make the latent abnormality clinically manifest. Nevertheless, the preparatory and triggering factors need not be separate or unrelated entities. A stressful acute upper respiratory infection, for example, could serve in both capacities.

While this article is focused on the nature of atopic abnormality in bronchial asthma, it is apparent that the same considerations may apply to other clinical manifestations of atopic allergy. As mentioned earlier, with the exception of nonnucleated erythrocytes, the adenyl cyclase system was found to be present

in all animal cells examined to date. Its ubiquitous character suggests, therefore, that the ultimate clinical manifestation of the fundamentally same atopic abnormality will be determined by the type of cell primarily involved, that is, by the specialized cell system of the multicellular organism which harbors primarily the postulated enzymatic abnormality (cells of bronchial tissue versus those of nasal mucosa, skin, or gastrointestinal tract).

THE SIGNIFICANT FACTS TO BE ACCOUNTED FOR BY ANY THEORY OF THE ATOPIC ABNORMALITY IN BRONCHIAL ASTHMA

Ideally an examination of evidence supporting the hypothesis just described should proceed following a clear and valid definition or characterization of the disease state itself. The latter may be defined on the basis of its established cause, functional or morphologic characteristics, or clinical manifestations. The cause of asthma is not known, and no single manifestation or combinations of criteria permit its precise definition at present. The term "asthma" is rarely used with the same connotation or defined in the same way by different authorities. Nevertheless, it is possible to assemble the most consistently prominent characteristics of this condition, and such a combination of criteria may be used as an analytical guide. Thus, it seems that any interpretation of the atopic abnormality in bronchial asthma will have to account for the following significant facts surrounding this condition:

1. The principal components of the pathophysiology of bronchial obstruction (smooth muscle spasm, edema, mucus hypersecretion, etc.).
2. The pharmacological abnormality.
3. The immunological abnormality.
4. The primary involvement of the bronchial tissue (the concept of the "shock organ").
5. Close association with respiratory infection.
6. Eosinophilia of common occurrence.
7. Increased tolerance to epinephrine.
8. Eminent therapeutic effectiveness of agents which are capable of restoring adrenergic action.
9. Susceptibility to a variety of unrelated precipitating factors.

The principal components of the pathophysiology of bronchial obstruction

The asthmatic episode is a disorder of paroxysmal labored breathing caused by an obstructive process in the bronchial tree. The characteristic wheezing and hyperinflation which occur reflect the obstructive process taking place, which in turn appears to be caused by a combination of bronchospasm, edema of the bronchial wall, and formation of thick tenacious plugs in the bronchial lumina.[4] By and large, the pathology of asthmatic obstruction can be explained by the normal effects of the immunologically or otherwise released pharmacological mediators. Two reasons, however, make it necessary to consider bronchial obstruction in the beta adrenergic frame of reference. First, asthma is distinguished not only by the release of these active agents but also by an enormously in-

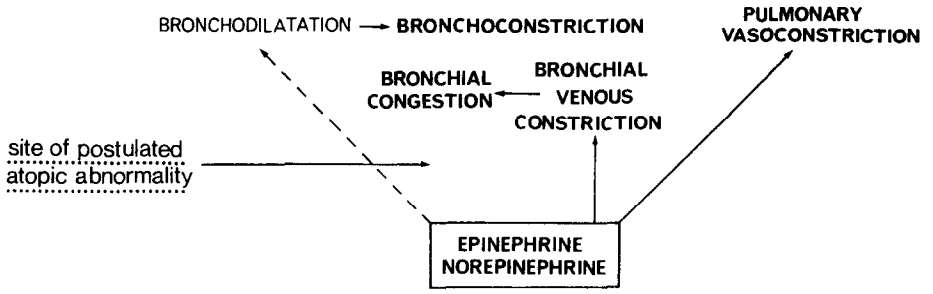

Fig. 3

Hypothetical schema of asthmatic responses to catecholamines under conditions of the postulated beta adrenergic blockade. Note the loss of adrenergic bronchodilator activity with subsequent prevalence of bronchial and venous constriction leading to airway obstruction.

creased bronchial reactivity to the released mediators.[5] Second, it must be examined whether the beta adrenergic theory can accommodate the types of alterations which are believed to make up the pathology of obstruction.

From what has been said on the dualistic receptor classification theory before, it is easy to see that if at the time of action of the endogenously released or exogenously administered catecholamines there is a shift in the relative availability of their two functionally antagonistic sets of specific receptors, the normal response to catecholamines will be quantitatively and qualitatively altered. For instance, in the bronchial tree the normal balance between the alpha adrenergic and beta adrenergic receptor systems appears to favor a beta adrenergic response, i.e., a relaxation of bronchial smooth musculature to epinephrine. If, however, the beta adrenergic receptors are blocked by a beta blocker, bronchoconstriction occurs instead of the usual relaxation.[84, 85] The possible implication of such an epinephrine reversal to asthmatic bronchospasm is obvious.

In the normal dog, both electric stimulation of the sympathetic accelerator nerve and injection of epinephrine or norepinephrine directly into the bronchial artery causes relaxation of the bronchial musculature but congestion of the bronchial mucosa by constriction of the bronchial veins.[86] Under circumstances of reduced bronchodilator activity of the catechols, it is possible that these vascular effects become more prominent and contribute to the development of edema (Fig. 3).[87] But even as far as the arterial portion of the mucosal vessels is concerned, it is known that exaggerated mucosal vasoconstriction is usually followed by the typical rebound, leading in essence to bronchial congestion and edema.[88]

In discussing vascular effects, the so-called fibrinoid degeneration of connective tissues and blood vessel walls, detectable occasionally also in asthmatic pulmonary tissue, can be duplicated by experimentally induced adrenergic imbalance (beta deficit or alpha dominance) through the production of inordinately severe arterial constrictions.[89-95] Regional decreases in pulmonary arterial blood flow during acute asthmatic attacks[96] and development of reversible segmental atelectasis[97] may also be compatible with such an adrenergic derangement. This

possibility may be indicated by findings implying that the adrenergic function receptor relationship in different vascular regions or in different portions of the regionally same vascular bed may be reversed[98, 99] or that different vascular segments may react independently to the same stimulus.[100]

No conclusive information is available as to whether bronchial secretion is inhibited by catecholamines,[98] and if it is, what is the receptor association of the effect or how may such an influence alter the normal secretion qualitatively. At this point, therefore, there is no way of knowing whether the abnormal bronchial secretions which occur in asthma can be integrated into the beta adrenergic theory.

The pharmacological abnormality

Asthmatic persons show a marked bronchial hypersensitivity to the endogenously released or exogenously administered pharmacological mediators of antigen-antibody responses even when the patient is completely asymptomatic at the time of testing (for a detailed discussion of the literature, see Szentivanyi and Fishel[5] and Szentivanyi and Katsh[11]). The cause of this hypersensitivity is not known, but available evidence indicates that it is not due to an impairment in the normal rapid detoxification of these agents or to some other abnormality in their metabolism.[101-103] Nor is it likely that this hyperreactivity is related to an enhanced histidine decarboxylase activity as postulated earlier,[137] since in animal experiments a marked increase in the enzymatic activity was shown to coexist with a normal sensitivity to pharmacological mediators.[80, 83]

Conversely, the evidence is unequivocal that pharmacological blockade of the beta adrenergic receptors is capable of inducing a hypersensitivity to histamine, serotonin, acetylcholine, bradykinin, and slow-reacting substance, regardless of whether these agents were released (formed) endogenously or administered exogenously.[5, 14, 18, 60, 76-79, 104-107, 135] All laboratory species which have been tested so far, i.e., mouse, rat, guinea pig, cat, and dog, were shown to be susceptible to sensitization by beta blockade, and such activity was found to be possessed by all the currently available specific beta blockers. Although within the same species there are substantial strain differences in susceptibility, it was found that a combination of beta blockade and of various procedures, conceivably resulting in additive blockade of beta or simultaneous stimulation of alpha, could invariably break strain resistance to sensitization.[79] Conversely, protection of susceptible strains was obtained through interventions known to protect beta receptors against development of a blockade, to bypass, or to eliminate an already established one. While alpha blockers did not show sensitizing activity, such properties of beta blockers were shown to be unrelated to their nonspecific effects, at least to those which have been documented so far. Likewise, no correlation was found between the antihistaminic-antiserotonin and the protective activities of alpha blockers against pertussis-induced hypersensitivity,[79] i.e., a condition which is currently considered to be caused by a beta blockade. Of further importance is the fact that sensitization by beta blockade is still effective after pithing the spinal cord and cutting the cervical vagus nerves. Also, the glycemic abnormality, which at present is believed to be the mediating mechanism of the

pharmacological hypersensitivity, can be reproduced in vitro by beta but not by alpha blockers.[81] Finally, recent extensive structure-activity comparisons designed to determine the structural requirements for sensitization by beta blocking agents showed that their sensitizing activity is specific, i.e., it is due to their ability to inhibit the beta pharmacological actions of the endogenously released adrenergic neurotransmitters or those of their exogenous counterparts.[139]

Among these findings, strategic importance may be attributed to the markedly enhanced reactivity of the anaphylactic guinea pig to inhalational antigen-challenge when, prior to aerosol exposure to the specific antigen, the animal is blocked beta adrenergically.[79] Since the immunologically released pharmacological mediators elicit respiratory changes in the guinea pig not unlike those in patients with bronchial asthma, the foregoing finding may represent a conceptual bridge to similar studies in human beings.

Indeed, beta adrenergic blockade has been shown to enhance bronchial reactivity to inhaled allergens[108] or to methacholine[140] in patients with seasonal allergic rhinitis without a previous history of bronchial asthma. By progressively increasing doses of the beta blocker, an acute airway obstruction could be produced which seemed to reach an intensity that may be found in patients with bronchial asthma.[140] Administration of beta blockers has also been reported[109, 203] to aggravate already existent asthmatic conditions and to cause precipitous and prolonged falls in forced one-second expiratory volume (FEV_1). Blockade of beta receptors was found to increase significantly the bronchial sensitivity of asthmatic subjects to methacholine, whereas no such effect was detectable in normal human subjects as judged by the change in FEV_1.[110] However, by using a more specific and sensitive measurement of airway resistance, the whole body plethysmograph method, a 50 to 100 per cent increase in airway resistance has been observed also in normal subjects in the first 30 minutes after the administration of a beta blocker.[111] It is important to note that in the latter experiments beta blockade was capable of producing airway obstruction, even without any simultaneous respiratory provocation such as exposure to histamine, methacholine, etc. These observations were confirmed by Besterman.[112, 113] Conversely, production of alpha adrenergic blockade has been reported to ameliorate asthmatic attacks in certain cases, as well as to reduce the observed hypersensitivity to exogenously administered histamine and cholinergic agents.[114, 115]

Three conclusions may be derived from these findings. First, the mammalian bronchial tree is in fact susceptible to sensitization by partial blockade of the beta adrenergic receptors. Second, of all "species" which have been examined so far, the human being with asthma appears to be the most susceptible to such sensitization. Third, the hypersensitivity so produced is manifested against representative members of a class of substances that could be broadly termed as the "pharmacological mediators" of antigen-antibody responses. Significance of these conclusions regarding the undetermined nature of the pharmacologic abnormality in asthma is seen in the fact that bacterial products may cause adrenergic alterations directionally identical to those produced by pharmacologic blockade of beta receptors.[18]

The immunological abnormality

Atopic persons, including those with asthma, react with an abnormal immune response to natural exposures to antigen. The nature of this abnormality is not known, but it appears to involve the production of an antibody, the so-called reagin or skin-sensitizing antibody, possessing distinct physicochemical and biological properties.

The production of reaginic antibody in these individuals is explained on the basis of a constitutional hyperresponsiveness to antigens in general, which results in the manufacture of large amounts of antibody including those of the reaginic variety, or as a qualitative abnormality in the immune apparatus which results in its production. An alternative hypothesis suggests that reaginic antibody is made by cells not usually engaged in antibody production but which are stimulated to do so against ingested or inhaled antigens by virtue of their strategic location in pulmonary or gastrointestinal tissues.[4]

Whatever the relative merits of these explanations may be, it is recalled that *Bordetella pertussis* causes not only a pharmacological hypersensitivity but alters the immune response both quantitatively (adjuvant) and qualitatively (production of "mast cell sensitizing antibodies"). The reasons for postulating that the same adrenergic lesion, which is believed to be the primary pathology in the pertussis-induced pharmacological hypersensitivity, may also be responsible for altering the antibody response, could be summarized as follows:

The purified component of the *B. pertussis* cell which is responsible for the histamine-sensitizing activity, the so-called histamine-sensitizing factor (HSF), was found to be either identical with or inseparable by a wide variety of procedures from the factor possessing the immunological adjuvant activity.[116-124] On the other hand, deprivation of the normal inhibition of glucose uptake, i.e., the type of adrenergic abnormality which is believed to be responsible for the pharmacological hypersensitivity in the whole animal, was shown to be reproducible in the isolated surviving rat diaphragm 60 minutes after the in vitro addition of HSF to the incubation medium.[81] In other words, the adrenergic abnormality could be reproduced in vitro by a principle of the bacterial cell which presently appears to be either identical with or inseparable from the factor possessing the adjuvant activity. Furthermore, in the same tissues in which HSF was found to increase the utilization of glucose, it was also shown to stimulate protein synthesis.[81]

It is also known that pertussis produces a striking increase in the rate of formation of lymphocytes in thymus, spleen, and lymph nodes,[125, 126] and it was shown that its ability to promote lymphocytosis closely resembles its capacity to produce pharmacological hypersensitivity.[127] Both activities are heat labile, require the same time to elicit maximum response, and both are markedly augmented by intravenous administration of pertussis vaccine as compared with other routes of administration.[127] Selective hyperplasia of lymphoid tissues has also been reported to be produced by chronic administration of a beta blocker,[128, 129] a finding which has been subsequently confirmed in our laboratory. Thus, both pertussis and pharmacologic beta blockade may produce prolifera-

tion of lymphoid elements, i.e., of cells which are believed to be mainly associated with antibody formation.[130] It is of great interest, therefore, that in a recent note the immunological adjuvant effect of beta adrenergic blockade has in fact been described.[131]

In this regard, it is to be noted that the rate of mitosis of the immunocompetent cells is a primary factor in determining the magnitude of antibody production.[132-136] An important factor affecting the rate of mitosis, at least in those mammalian cells which have been studied in detail, is the energy supply of the cell. This in turn depends primarily on the intracellular availability of glucose derivatives.[141, 142] Hormones which are capable of stimulating or inhibiting particular rate-limiting reactions in the intermediary metabolism of carbohydrates are also capable of influencing mitotic activity. Insulin, which stimulates the peripheral (extrahepatic) uptake of glucose, also increases the rate of mitosis.[143] Conversely, epinephrine which inhibits the peripheral uptake of glucose, also inhibits mitosis.[144-148] In fact, of all the substances which are capable of inhibiting mitotic activity, epinephrine is one of the most active (Bullough and Laurence[146-148]). The rate-limiting factor of mitosis, therefore, may be the rate of entry of glucose into the cell. In the beta adrenergically blocked mouse a striking increase in the normal rate of entry of glucose into several extrahepatic tissues was found, and the spleen, a prominent lymphoid tissue, was among them.[78] Thus, beta adrenergic blockade could conceivably produce proliferation of the immunocompetent cells by preparing them to meet the high energy requirements of increased mitotic activity through the elimination of the normal adrenergic inhibition of glucose uptake.

Since in most areas of adrenergic activity the alpha and beta receptor systems are functionally associated with antagonistic responses, one would expect that alpha blockade would result in a suppression of mitotic activity in immunocompetent cells. No evidence is available that this is indeed the case. Nevertheless, it may be noted that the most specific alpha blockers, the haloalkylamines, are chemically related to the nitrogen mustards and similar immunosuppressive agents; like the latter, the tertiary amine cyclizes to form a reactive ethyleni-

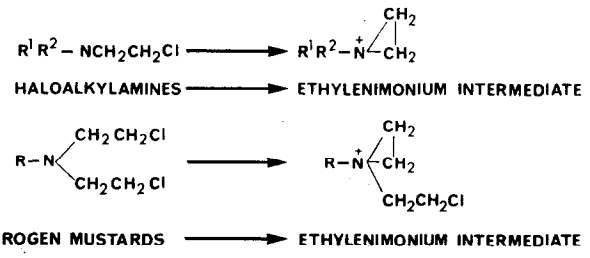

Fig. 4

Schema depicting the similar chemical reactivities of the haloalkylamines (alpha adrenergic blocking agents) and the nitrogen mustards (immunosuppressive agents). The tertiary amine cyclizes to form a reactive ethylenimonium intermediate, the formation of which is critical for specific blocking activity at the alpha site. Likewise, formation of the ethylenimonium ion constitutes the initial reaction of the nitrogen mustards.

monium intermediate (Fig. 4), the formation of which appears to be critical for specific blocking activity at the alpha site.[149-151] Similarly, formation of the ethylenimonium ion constitutes the initial reaction of the nitrogen mustards.[152] It may be significant, therefore, that a partial suppression of the immunological adjuvant effect of pertussis vaccine by alpha adrenergic blockade was recently observed.[124]

With this information in mind, it seems permissible to postulate that the adrenergic lesion of the pertussis-induced hypersensitive state, which is believed to be responsible for the pharmacological hypersensitivity, may also be the cause of the quantitative and qualitative alterations of the immune response seen in this condition. In a similar way, the autonomic derangement responsible for the pharmacologic hypersensitivity in asthma may also account for the immunological abnormality. In the beta adrenergic frame of reference, this would mean that deprivation of the normal beta adrenergic inhibition of glucose uptake causes certain cells of the bronchial tree to be stimulated to produce antibody upon natural exposures of usually innocuous antigens.

The primary involvement of the bronchial tissue (the concept of the "shock organ")

Bronchial asthma was defined as a unique pattern of bronchial hyperreactivity to various stimuli. Implicit in this definition is the localized character (bronchial) of the hyperreactivity. Likewise, all other manifestations of atopic allergy (hay fever, perennial allergic rhinitis, atopic dermatitis, chronic urticaria, or angioneurotic edema, etc.) may be regarded as "localized" hyperreactivities.

Immunologic theories of atopic disease are usually silent about the possible significance of this selective involvement, or the older literature simply recognizes it as a problem of the "shock organ." This terminology, and the ideas related to it, is borrowed from the historical anaphylactic analogy. They refer to the leading organ-response in anaphylactic phenomena, which appears to be determined by the site of the antigen-antibody interaction (i.e., skin in local anaphylaxis) or by certain anatomical characteristics of the test-species (e.g., the "obstruction-apparatus" in the smooth musculature of canine hepatic veins in systemic anaphylaxis). The more modern literature has considered additional factors, some of which may also be operative in determining the shock tissue in question (for a detailed analysis see Filipp and Szentivanyi[204]).

None of these ideas, however, seem to satisfactorily explain why, for instance, one person reacts with hay fever and another with asthma to the same inhaled allergen. Nor is it explained why the pharmacological hypersensitivity is limited to the target cells of one or more tissues instead of affecting all the target cells uniformly. In asthmatic patients, for example, the injection of an otherwise nontoxic amount of histamine induces wheezing but not hives. In individuals with chronic urticaria, it induces hives but not wheezing. In atopic dermatitis the histamine flush appears at the cutaneous sites of characteristic predilection whether or not the disease is active at the time of testing.[5]

The beta adrenergic theory proposes that the ultimate clinical manifestation

of the atopic abnormality, i.e., the organ or tissue localization of the disease, is determined by the type of cell systems primarily harboring the postulated enzymatic abnormality. The demonstration that a pharmacologic blockade of beta receptors may enhance bronchial reactivity to inhaled allergens or methacholine in hay fever patients without a previous history of bronchial asthma is highly compatible with this postulate.[108, 140] These findings may be interpreted to mean that an acute bronchial blockade of beta receptors shifted the clinical response from pure hay fever to bronchial asthma.

Similarly, depending on the relative involvement of the various specialized cell systems (antibody producing cells, smooth muscle cells, gland cells, epidermis, and eosinophils, etc.) in a particular case, individual variations may occur in the final clinical make-up of any of the atopic manifestations.

Close association with respiratory infection

The beta adrenergic theory may also explain the nature of the close relation between respiratory infection and asthma, whether the role of infection is immunological, pharmacodynamic, or both. As has been reviewed in detail, adrenergic imbalance can be produced not only by the HSF of pertussis but also by bacterial endotoxins. Other microbial products are also known to cause less defined but nevertheless profound disturbances in autonomic regulation.[18, 205, 206] In this connection no information is available at present on viruses. However, it is perfectly possible that viral invasion of adrenergic target cells could also produce the postulated enzymatic lesion. For instance, viruses in infecting the adrenergic target cells may impose themselves on the genetic apparatus of those cells. Such viral parasitism near the genetic level of the adrenergic target cell may conceivably result in the production of defective adenyl cyclase molecules unfit for effective combination with the endogenously released or exogenously administered catecholamines.

Of these microbial products, the endotoxins deserve special consideration. Although they are generally considered to be produced only by gram-negative microorganisms, materials with similar properties may be found in gram-positive bacteria[153, 154] and in a variety of plant and animal tissues as well.[155-157] Therefore, endotoxins and substances with similar pharmacodynamic activity are likely to participate in many of the respiratory infections associated with asthma. The possible significance of their presence will be appreciated when it is recalled that endotoxins are not only potent releasers of the amine mediators but also potent sensitizers of the adrenergic target cells (in an alpha position) to the catecholamines so released.[18] For instance, when an animal is given an intravenous injection of 1 μg of purified endotoxin, followed at any time during the next 4 hours by the intradermal injection of 10 μg of epinephrine or norepinephrine, hemorrhagic necrosis of considerable proportions developes at the injected site. In contrast, no evidence of tissue destruction can be detected when even as large a dose as 100 to 200 μg of epinephrine is repeatedly injected into the same skin site of a normal member of the same species.[158] That this lesion is due not to the systemic activity of endotoxin but to its local effect is demonstrated by the intradermal injection of an endotoxin-epinephrine

mixture which is capable of producing the same hemorrhagic necrosis. In these circumstances the endotoxin is not absorbed and has no opportunity to act systemically.

A better insight into the mechanism of this necrotizing activity can be obtained using the isolated rabbit ear for measuring resistance to perfused fluid and by studying the reactions of terminal vessels in the exteriorized mesoappendix of the rat. For instance, perfusion of a small amount of endotoxin (0.5 μg) into the isolated rabbit ear is followed within a few minutes by a 200- to 800-fold increase in the vasoconstrictor response to epineprine. Similarly, even a 1,000-fold potentiation of epinephrine activity by endotoxin can be seen to occur in the mesoappendix.[159]

At the receptor level, such an abnormal response could be due either to a hypersensitivity of the alpha or to a functional deficiency of the beta receptor system. A comparison of the in vitro responsiveness of arterial strips from endotoxin-treated versus normal rabbits to chemical and electrical stimuli suggests that the lesion is associated with the relaxation mechanism of the cell.[160] This would seem to argue for a beta adrenergic localization of the lesion. Indeed, lesions grossly resembling the endotoxin-induced "epinephrine-lesion" already described may be produced in the skin of both guinea pigs and rabbits following the injection of a mixture of beta blocker and epinephrine.[77] Conversely, the local Shwartzman reaction is inhibited by alpha[161] but not by beta blockade.[162] Also the generalized form of this reaction can be inhibited by alpha blockers[163] as well as by making the test animal epinephrine tolerant.[164]

The principal pathology of the generalized Shwartzman phenomenon is the bilateral cortical necrosis of kidneys. Development of this lesion is thought to be related to an alteration in plasma fibrinogen, i.e., to the appearance of the so-called "heparin-precipitable fibrinogen" (HPF), with subsequent deposition of this material in glomerular capillary loops causing obstruction and resulting in renal necrosis.[158] In accord with this, inhibition of the generalized Shwartzman reaction by epinephrine tolerance was found to be related to prevention of development of the HPF in the plasma.[164]

While it is not known whether endotoxins produce a similar adrenergic lesion on vascular smooth muscle of the asthmatic patient, it is difficult to ignore the tempting analogy between these animal findings and the already mentioned occurrence of fibrinoid degeneration of connective tissue and blood vessel walls in the allergic state.[165-177] Furthermore, the functional associations of adrenergic receptors of vascular smooth muscle seem to parallel those of bronchial smooth muscle within the same species.[178] It is possible, therefore, that endotoxins are also adrenergically active on human bronchial muscle.

However, regardless of the nature of the pharmacologically active microbial agent in a given case, the fact remains that infection of the respiratory tract is known to increase bronchial reactivity of both normal and asthmatic individuals to pharmacologic mediators.[5] Development of such a hypersensitivity is not likely to be caused by a nonspecific inflammatory effect, since administration of killed influenza vaccine, which has no local inflammatory activity, was also shown to produce pharmacological hypersensitivity.[179] Finally, it has been

recently observed that patients with chronic bronchitis, who never had an asthmatic episode before, experienced acute asthmatic attacks during therapy with a beta blocker instituted for some unrelated reason.[112, 113]

Eosinophilia of common occurrence

A peculiar distinction of eosinophils is their conspicuous association with allergic reactions, including asthma. However, the nature of this association and their role in allergic events remain to be clarified.

Of the catecholamines, both epinephrine and isoproterenol produce eosinopenia, whereas norepinephrine has no such effect. The eosinopenic effect of catechols is blocked by dichloroisoproterenol and by propranolol but not by dibenamine.[180] These operations define eosinopenia as a beta adrenergic action of catecholamines. Consequently, an impairment of beta adrenergic mechanisms would be expected to eliminate one of the most important suppressing influences in the homeostatic control of eosinophils and possibly result in eosinophilia.

It is of interest, therefore, that a recent comparison of the effect of epinephrine on circulating eosinophils of normal and asthmatic subjects showed a significantly reduced eosinopenic response in asthmatic subjects.[181] This may indicate that the beta adrenergic mechanisms are in fact impaired in asthmatic persons, and eosinophilia in asthma may be, in part, a result of this abnormality.

Increased tolerance to epinephrine

It has long been believed that asthmatic persons are somehow more tolerant to epinephrine than other individuals.[5, 184] This impression has recently gained some experimental support by observations of reduced asthmatic responsiveness to catechols as measured by various systemic parameters of adrenergic reactivity,[181, 185-188, 190] though some of these findings are not corroborated in 2 other studies.[189, 207]

Space does not permit a detailed analysis of the relative merits and shortcomings of these studies. For our purpose here, the important point is that with increasing severity of the asthmatic condition a marked resistance to the bronchial and to some of the systemic activities of epinephrine may in fact be seen. In status asthmaticus, the majority of patients are "fast" to epinephrine.[184] Indeed, status asthmaticus is sometimes defined as persistent severe refractory asthma, which is epinephrine resistant.[191] These observations are in harmony with the idea expressed earlier that it is only when a continuing series of adaptive responses is demanded of the adrenergically incapacitated bronchial tissue that the postulated defect becomes readily manifest.

"Epinephrine fastness" cannot be explained by tachyphylaxis, because in bronchial preparations no such development can be seen after repeated exposure to epinephrine.[87] Nor can mechanical obstruction adequately account for the phenomenon, since in most cases the bronchodilator activity of theophylline derivatives is retained and there are cases of epinephrine fastness without evidence of substantial obstruction.[5] Restoration of epinephrine responsiveness by correction of respiratory acidosis does not establish a causal relationship,[192-194]

since no consistent correlation could be found to exist between epinephrine fastness and acidosis.[191, 195, 196]

On the other hand, the very existence of the phenomenon of epinephrine fastness may itself be an excellent argument for the beta adrenergic theory. The potential strength of this argument will become more evident when the pharmacodynamics of those drugs or procedures are considered which are still relatively effective in this condition.

Eminent therapeutic effectiveness of agents which are capable of restoring adrenergic action

It seems that these drugs or therapeutic interventions are capable of restoring normal adrenergic action by either (1) bypassing the biochemical site of the postulated beta adrenergic lesion or (2) sensitizing the beta receptors, i.e., lowering the receptor-threshold to catecholamine action.

Aminophylline or other methylxanthines would seem to be representatives of the first category of drugs. These agents are potent inhibitors of phosphodiesterase, which is the enzyme responsible for the inactivation of 3′, 5′-AMP. Since current thinking would place this point beyond the receptor-activation step, it is possible that the effectiveness of these drugs in epinephrine fast individuals and other asthmatic persons is due to their capability of producing adrenergic action by a bypass of the site of the postulated beta adrenergic blockade (Fig. 5). The type of correlation found between the phosphodiesterase-inhibitory and anti-asthmatic potencies of the various methylxanthines is highly compatible with this interpretation.[201, 202]

The glucocorticoids could be regarded as representatives of the second cate-

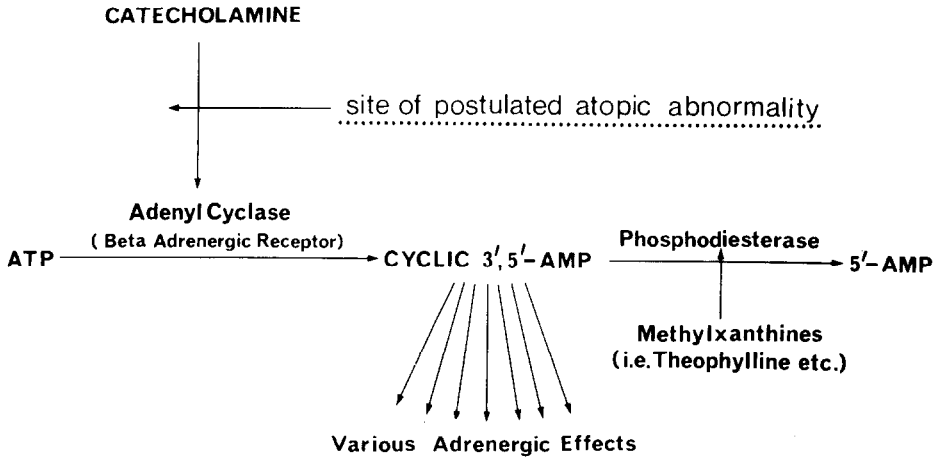

Fig. 5

Schema of restoration of normal adrenergic action by methylxanthine-derivatives (aminophylline, theophylline, etc.) through a bypass of the site of the postulated beta adrenergic blockade.

gory of drugs. Their value in asthma is commonly attributed to their general anti-inflammatory activity, though nothing more specific is known about the molecular mechanism of this anti-inflammatory activity. On the other hand, the corticosteroids are known to support the normality of the target cell responses to catecholamines, and it is well established that in the absence of glucocorticoids the receptor-threshold for catecholamines may be raised, occasionally up to the point of complete unresponsiveness.[197-199] Therefore, corticosteroid deprivation can clinically simulate either an indiscriminate or a selective adrenergic blockade, depending on the types of effector responses tested.[4, 197] Conversely, even a pharmacologically established beta adrenergic blockade in an intact animal, i.e., in an organism where normal concentrations of steroids must be presumed to have been present, could be overcome with an excessive amount of glucocorticoid administered exogenously.[14] This indicates that the glucocorticoids are capable of sensitizing the adrenergic target cells to the action of catecholamines. It is of further importance that neither the anti-inflammatory nor the catechol-potentiating activities of the steroid molecule are separable from its glucocorticoid properties.[200] These considerations bring sharply into focus the possibility that the beneficial effects of steroids in epinephrine fast and other asthmatic individuals are due to their action on the beta adrenergic receptors.

The same could apply to the previously mentioned restoration of epinephrine responsiveness in asthmatic patients by the administration of sodium lactate or bicarbonate, the mechanism of which cannot be attributed to the correction of respiratory acidosis since many of these cases show normal or alkaline pH.[191, 195, 196] Effectiveness of these procedures is more easily explicable, therefore, by sensitization of the adrenergic receptors to catecholamines.

Susceptibility to a variety of unrelated precipitating factors

In addition to the antigen-antibody interaction, asthmatic episodes are known to be triggered by a large variety of stimuli such as infection, various synthetic and natural chemicals, conditioned reflexes, psychic stimuli, changes in atmospheric pressure, inhalation of cold air, nonantigenic dusts, fumes, and other irritants, etc. Any molecular interpretation of a susceptibility to such a large variety of unrelated stimuli would appear to necessitate the postulate that the primary lesion be connected with a final common pathway operating through a biologically unusually broad messenger system.

The adenyl cyclase - 3′, 5′-AMP system is the first known messenger system capable of responding to a wide variety of neurohumoral and hormonal agents subserving homeostasis. This unusually broad reactive capacity of the system may be explained by the latest hypothetical model of the enzyme.[31] In this model, adenyl cyclase is pictured as a single protein extending from one side of the cell membrane to the other and being composed of two functional subunits. One is a regulatory subunit facing the extracellular space, whereas the other is a catalytic subunit, the active center of which is in contact with the cell interior. The neurohumor or hormone interacts with the regulatory subunit, and this interaction will influence the configuration of the catalytic subunit which in turn will regulate the rate of synthesis of 3′, 5′-AMP, the intracellular messenger.

From a cybernetic point of view, 3′, 5′-AMP as a common messenger could represent a target molecule in a set of intracellular informational signals involved in the transduction of environmental information.[182]

Thus, the adenyl cyclase - 3′, 5′-AMP system would ideally fit the qualifications of the postulate that the biochemical lesion of the atopic abnormality must be connected with a final common pathway operating through a biologically unusually broad homeostatic messenger system.

REFERENCES

1. Rackemann, F. M.: Clinical Allergy Particularly Asthma and Hay Fever. Mechanism and Treatment, New York, 1931, The Macmillan Company, p. 3.
2. Szentivanyi, A., Filipp, G., and Legeza, I.: Investigations on Tobacco Sensitivity, Acta. med. Acad. Sc. hung., Tomus III, Fasciculus 2., 175, 1952.
3. Szentivanyi, A., Filipp, G., and Legeza, I.: Dohanyallergias vizsgalatok. A dohanyallergia, mint impari artalom, Orv. hetil. **44**: 1, 1951.
4. Pearlman, D. S., and Szentivanyi, A.: Excessive Reactivity of Defense Mechanisms-Allergy, *in* Cooke, R. E., editor: The Biologic Basis of Pediatric Practice, New York, 1968, McGraw-Hill Book Company, Inc., pp. 536-546.
5. Szentivanyi, A., and Fishel, C. W.: Die Amin-Mediatorstoffe der Allergischen Reaktion und die Reaktionsfahigkeit ihrer Erfolgszellen, *in* Filipp, G., editor: Pathogenese und Therapie Allergischer Reaktionen. Grundlagenforschung und Klinik, Stuttgart, 1966, Ferdinand Enke Verlag, pp. 588-683.
6. Szentivanyi, A.: The Reciprocal Histamine-Adrenaline "Counterregulation"—A Physiological Interplay, Presented at the Annual Dinner of the Rocky Mountain Allergy Society, Feb. 21, 1962, Denver, Colo.
7. Szentivanyi, A.: The Biochemical Pharmacology of Adrenergic Action as Related to the Pathogenesis of Bronchial Asthma, Ann. Allergy **24**: 253, 1966.
8. Szentivanyi, A.: Bacterial Hypersensitivity in Relation to Bronchial Obstruction, Presented at Symposium on "New Approaches to Study of Clinical Manifestations of Human Infection and Allergy," The National Institute of Allergy and Infectious Diseases, Bethesda, Md., Oct. 22, 1966.
9. Szentivanyi, A.: Adrenergic Pharmacology and the Pathogenesis of Bronchial Asthma, Presented at Symposium on "Research in Asthma and Other Allergic Disorders," Sponsored by United States Dept. of Health, Education and Welfare, National Jewish Hospital, Denver, Colo., April 7, 1967.
10. Szentivanyi, A.: The Beta Adrenergic Theory of Bronchial Asthma: An Alternative to the Classical Concept, Presented at the Pre-Congress Seminar of The American College of Allergists, Denver, Colo., March 25, 1968.
11. Szentivanyi, A., and Katsh, S.: Immunopharmacology. The Pharmacological Mediation of Antigen-Antibody Responses, New York, Paul B. Hoeber, Inc. In press.
12. Satake, Y.: Secretion of Adrenaline and Sympathins, Hongo, Tokyo, Japan, 1955, Nanzando Company Ltd., p. 158.
13. Hagen, P.: The Storage and Release of Catecholamines, Pharmacol. Rev. **11**: 361, 1959.
14. Szentivanyi, A., Fishel, C. W., and Talmage, D. W.: Adrenaline Mediation of Histamine and Serotonin Hyperglycemia in Normal Mice, and the Absence of Adrenaline-Induced Hyperglycemia in Pertussis-Sensitized Mice, J. Infect. Dis. **113**: 86, 1963.
15. Rocha e Silva, M.: The Physiological Significance of Bradykinin, Ann. New York Acad. Sc. **104**: 190, 1963.
16. Greef, K., and Heeg, E.: Die anaphylaktische Reaktion perfundierter Herzpraparate, isolierter Herzvorhofpreparate, und isolierter Papillarmuskeln, verglichen mit der Wirkung des Histamins und Noradrenalins, Archs. internat. pharmacodyn. **149**: 136, 1964.
17. Flacke, W., Atanackovic, D., Gillis, R. A., and Alper, M. H.: The Actions of Histamine on the Mammalian Heart, J. Pharmacol. & Exper. Therap. **155**: 271, 1967.
18. Szentivanyi, A., and Fishel, C. W.: Effect of Bacterial Products on Responses to the Allergic Mediators, *in* Samter, M., editor: Immunological Diseases, Boston, 1965, Little, Brown & Company, pp. 226-241.
19. Lockett, M. F.: Identification of an Isoprenaline-Like Substance in Extracts of Adrenal Glands, Brit. J. Pharmacol. **9**: 498, 1954.
20. Lockett, M. F.: The Transmitter Released by Stimulation of the Bronchial Sympathetic Nerves of Cats, Brit. J. Pharmacol. **12**: 86, 1957.
21. Eakins, K. E., and Lockett, M. F.: The Formation of An Isoprenaline-Like Substance from Adrenaline, Brit. J. Pharmacol. **16**: 108, 1961.

22. Ahlquist, R. P.: A Study of the Adrenotropic Receptors, Am. J. Physiol. **153**: 586, 1948.
23. Furchgott, R. F.: Receptors for Sympathomimetic Amines, *in* Vane, J. R., Wolstenholme, G. E. W., and O'Connor, M., editors: Ciba Foundation Symposium on Adrenergic Mechanisms, Boston, 1960, Little, Brown & Company, pp. 246-252.
24. Furchgott, R. F.: The Pharmacological Differentiation of Adrenergic Receptors, Ann. New York Acad. Sc. **139**: 553, 1967.
25. Moran, N. C.: The Development of Beta Adrenergic Blocking Drugs: A Retrospective and Prospective Evaluation, Ann. New York Acad. Sc. **139**: 649, 1967.
26. Belleau, B.: Stereochemistry of Adrenergic Receptors: Newer Concepts on the Molecular Mechanism of Action of Catecholamines and Antiadrenergic Drugs at the Receptor Level, Ann. New York Acad. Sc. **139**: 580, 1967.
27. Belleau, B.: Steric Effects in Catecholamine Interactions with Enzymes and Receptors, Pharmacol. Rev. **18**: 131, 1966.
28. Sutherland, E. W., and Rall, T. W.: The Relation of Adenosine-3′,5′-Phosphate and Phosphorylase to the Actions of Catecholamines and Other Hormones, Pharmacol. Rev. **12**: 265, 1960.
29. Sutherland, E. W., Øye, I., and Butcher, R. W.: The Action of Epinephrine and the Role of Adenyl Cyclase System in Hormone Action, Recent Progr. Hormone Res. **21**: 623, 1965.
30. Sutherland, E. W., and Robison, G. A.: The Role of Cyclic-3′,5′-AMP in Responses to Cathecholamines and Other Hormones, Pharmacol. Rev. **18**: 145, 1966.
31. Robison, G. A., Butcher, E. W., and Sutherland, E. W.: Adenyl Cyclase as an Adrenergic Receptor, Ann. New York Acad. Sc. **139**: 703, 1967.
32. Bulbring, E.: Biophysical Changes Produced by Adrenaline and Noradrenaline, *in* Vane, J. R., Wolstenholme, G. E. W., and O'Connor, M., editors: Ciba Foundation Symposium on Adrenergic Mechanisms, Boston, 1960, Little, Brown & Company, pp. 275-287.
33. Bueding, E., and Bulbring, E.: The Inhibitory Action of Adrenaline. Biochemical and Biophysical Observations, *in* Bulbring, E., editor: Pharmacology of Smooth Muscle, New York, 1964, The Macmillan Company, pp. 37-56.
34. Davoren, P. R., and Sutherland, E. W.: The Cellular Location of Adenyl Cyclase in the Pigeon Erythrocyte, J. Biol. Chem. **238**: 3016, 1963.
35. Sutherland, E. W., Davoren, P., and Makman, R.: The Cellular Location of Adenyl Cyclase and Adenosine-3′,5′-Phosphate in Escherichia coli, *in* Whelan, W. J., and Cameron, M. P., editors: Ciba Foundation Symposium on Control of Glycogen Metabolism, Boston, 1964, Little, Brown & Company, pp. 233-243.
36. Rabinowitz, M., DeSalles, L., Meisler, J., and Lorand, L.: Distribution of Adenyl Cyclase Activity in Rabbit Skeletal Muscle Fractions, Biochim. et biophys. acta **97**: 29, 1965.
37. Sutherland, E. W., Rall, T. W., and Menon, T.: Adenyl Cyclase. I. Distribution, Preparation, and Properties, J. Biol. Chem. **237**: 1220, 1962.
38. Murad, F., Chi, Y. M., Rall, T. W., and Sutherland, E. W.: Adenyl Cyclase. III. The Effect of Catecholamines and Choline Esters on the Formation of Adenosine 3′,5′-Phosphate by Preparations From Cardiac Muscle and Liver, J. Biol. Chem. **237**: 1233, 1962.
39. Vaughan, M.: The Mechanism of the Lipolytic Action of Catecholamines, Ann. New York Acad. Sc. **139**: 841, 1967.
40. Butcher, R. W.: Cyclic 3′,5′-AMP and the Lipolytic Effects of Hormones on Adipose Tissue, Pharmacol. Rev. **18**: 237, 1966.
41. Lundholm, L., and Mohme-Lundholm, E.: The Action of Adrenaline on Carbohydrate Metabolism in Relation to Some of Its Pharmacodynamic Effects, *in* Vane, J. R., Wolstenholme, G. E. W., and O'Connor, M., editors: Ciba Foundation Symposium on Adrenergic Mechanisms, Boston, 1960, Little, Brown & Company, pp. 305-322.
42. Dobbs, J. W., and Robison, G. A.: Functional Biochemistry of Beta Receptors in the Uterus, Fed. Proc **27**: 352, 1968.
43. Meltzer, S. J.: Bronchial Asthma as a Phenomenon of Anaphylaxis, J. A. M. A. **55**: 1021, 1910.
44. Frick, O. L.: The Atopic State—A Particular Kind of Immune Reaction. A Review, Ann. Allergy **24**: 95, 1966.
45. Filipp, G., Szentivanyi, A., and Mess, B.: Anaphylaxis and the Nervous System, Acta med. Acad. Sc. hung., Tomus III, Fasciculus 2., 163, 1952.
46. Filipp, G., and Szentivanyi, A.: Experimentelle Data zur regulativen Rolle des Neuroendokriniums in experimenteller Anaphylaxie I. Relazioni e Communicazioni, 229, Rome, Il Pensiero Scientifico, 1956.
47. Filipp, G., and Szentivanyi, A.: Anaphylaxis and the Nervous System, Part III, Ann. Allergy **16**: 306, 1958.
48. Szentivanyi, A., and Filipp, G.: Die Wirkung von Hypothalamuslasionen an den

anaphylactischen Schock des Meerschweinchens, Allergie und Asthma, Band **1**: 23, 1957.
49. Szentivanyi, A., and Filipp, G.: Anaphylaxis and the Nervous System, Part II, Ann. Allergy **16**: 143, 1958.
50. Szentivanyi, A., and Szekely, J.: Experimentelle Data zur regulativen Rolle des Neuroendokriniums in experimenteller Anaphylaxie I. Relazioni e Communicazioni, 237, Rome, Il Pensiero Scientifico, 1956.
51. Szentivanyi, A., and Szekely, J.: Effect of Injury to and Electrical Stimulation of Hypothalamic Areas on the Anaphylactic and Histamine Shock of Guinea Pig, Ann. Allergy **14**: 259, 1956.
52. Szentivanyi, A., and Szekely, J.: Uber den Effect der Schadigung und der elektrischen Reizung der Hypothalamischen Gegenden auf den anaphylactischen und Histamin-Schock des Meerschweinchens, Allergie und Asthma, Band **1**: 29, 1957.
53. Szentivanyi, A., and Szekely, J.: Wirkung der konstanten Reizung hypothalamischer Strukturen durch Tiefenelektroden auf den histaminbedingten und anaphylaktischen Schock des Meerschweinchens, Acta physiol. hung. Suppl. Tomus **XI**: 41, 1957.
54. Szentivanyi, A., and Szekely, J.: Anaphylaxis and the Nervous System, Part IV, Ann. Allergy **16**: 389, 1958.
55. Gellhorn, E.: Autonomic Imbalance and the Hypothalamus, Minneapolis, 1957, University of Minnesota Press.
56. Korneva, E. A., and Khai, L. M.: Influence of Hypothalamic Lesions on Antibody Production, Fiziol. zhur. SSSR. **49**: 42, 1963.
57. Luparello, T. J., Stein, M., and Park, D. C.: Effect of Hypothalamic Lesions on Rat Anaphylaxis, Am. J. Physiol. **207**: 911, 1964.
58. Kind, L. S.: The Altered Reactivity of Mice After Inoculation With *Bordetella pertussis* Vaccine, Bact. Rev. **22**: 173, 1958.
59. Sanyal, R. K., and West, G. B.: Sensitizing Properties of *Hemophilus pertussis* Vaccine in Laboratory Animals, Internat. Arch. Allergy **14**: 241, 1959.
60. Malkiel, S., and Hargis, B. J.: Sensitization of the Mouse to Bradykinin, Proc. Soc. Exper. Biol. & Med. **125**: 565, 1967.
61. Sugiyama, S.: Cited by, Takino, M., and Takino, Y.: Self-Regulation of the Parasympathetic Nervous System Based on Variety of Allergic Phenomena and its Relation to the Parasympathicus, Acta neuroveg. **22**: 15, 1961.
62. Denchev, V., and Kosturkov, G.: Studies of the Development and Mechanism of Increased Tolerance to Adrenalin in Mice Immunized with *Bordetella pertussis* Vaccine, Ztschr. Immunitätsforschg. **131**: 247, 1966.
63. Munoz, J., and Schuchardt, L. F.: Effect of *Hemophilus pertussis* on Sensitivity of Mice to Cold Stress, Proc. Soc. Exper. Biol. & Med. **94**: 186, 1957.
64. Kind, L. S., and Gadsden, R. H.: Adrenal Function Tests in Mice Sensitized to Histamine with *Hemophilus pertussis* Vaccine, Proc. Soc. Exper. Biol. & Med. **84**: 373, 1953.
65. Fairchild, E. J., Bobb, G. A., and Thompson, G. E.: Enhanced Toxicity of a Respiratory Irritant (Ozone) by Pertussis Sensitization, Fed. Proc. **25**: 692, 1966.
66. Munoz, J.: Hypersensitivity Reactions Induced in Mice Treated with *Bordetella pertussis, in* Landy, M., and Braun, W., editors: Bacterial Endotoxins, New Brunswick, 1964, Rutgers University Press, pp. 460-473.
67. Munoz, J.: Effect of Bacteria and Bacterial Products on Antibody Response, Advances Immunol. **4**: 397, 1964.
68. Mota, I.: Mast Cells and Anaphylaxis, Ann. New York Acad. Sc. **103**: 264, 1963.
69. Mota, I.: Mast Cell Lytic Antibodies, Nature **192**: 1201, 1961.
70. Mota, I.: Failure of Rat and Rabbit Antiserum to Passively Sensitize Normal and Pertussis-Treated Rats and Mice so as to Induce Mast Cell Damage and Histamine Release on Later Contact with Antigen, Immunology **5**: 11, 1962.
71. Mota, I.: The Mechanism of Anaphylaxis. I. Production and Biological Properties of "Mast Cell Sensitizing" Antibody, Immunology **7**: 681, 1964.
72. Mota, I.: The Mechanism of Anaphylaxis. II. The Role of "Mast Cell Sensitizing" Antibody and Delayed Hypersensitivity in Rat Anaphylaxis, Immunology **7**: 700, 1964.
73. Austen, K. F., and Humphrey, J. H.: In Vitro Studies of the Mechanisms of Anaphylaxis, Advances Immunol. **3**: 1, 1963.
74. Kind, L. S., and Richard, W. W.: Local and Systemic Anaphylaxis in the Pertussis-Inoculated Mouse, Nature **202**: 309, 1964.
75. Tjabbes, T., and DeWied, D.: The Influence of Ventral Posterior Hypothalamus on *Bordetella pertussis* Vaccine-Induced Eosinophilia, Arch. internat. pharmacodyn. **135**: 218, 1962.
76. Fishel, C. W., Szentivanyi, A., and Talmage, D. W.: Sensitization and Desensitization of Mice to Histamine and Serotonin by Neurohumors, J. Immunol. **89**: 8, 1962.
77. Fishel, C. W., Szentivanyi, A., and Talmage, D. W.: Adrenergic Factors in *Bordetella*

pertussis-Induced Histamine and Serotonin Hypersensitivity of Mice, *in* Landy, M., and Braun, W., editors: Bacterial Endotoxins, New Brunswick, 1964, Rutgers University Press, pp. 474-481.
78. Fishel, C. W., and Szentivanyi, A.: The Absence of Adrenaline-Induced Hyperglycemia in Pertussis-Sensitized Mice and Its Relation to Histamine and Serotonin Hypersensitivity, J. ALLERGY **34**: 439, 1963.
79. Townley, R. G., Trapani, I. L., and Szentivanyi, A.: Sensitization to Anaphylaxis and to Some of Its Pharmacological Mediators by Blockade of the Beta Adrenergic Receptors, J. ALLERGY **39**: 177, 1967.
80. Katsh, S., and Szentivanyi, A.: Dissociation of the Histamine-Sensitizing and Histidine Decarboxylase-Enhancing Activities of the *Bordetella pertussis* Cell, J. ALLERGY **41**: 106, 1968.
81. Szentivanyi, A., Katsh, S., and Townley, R. G.: Effect of Pertussis Sensitization and Pharmacological Beta-Adrenergic Blockade on the In Vitro Uptake of D-Glucose-2-C^{14} Into Glycogen of Diaphragm and Upon the Formation of $C^{14}O_2$ From Glucose-1-C^{14} by Adipose Tissue, J. ALLERGY **41**: 107, 1968.
82. Townley, R. G., and Szentivanyi, A.: Secretion of Immunoreactive Insulin (IRI) by the Isolated Perfused Pancreas of Normal and Pertussis-Sensitized Rats, J. ALLERGY **41**: 122, 1968.
83. Szentivanyi, A., Katsh, S., and McGarry, B.: Lack of Correlation Between the Histamine Sensitizing and Histidine Decarboxylase Activating Effects of *Bordetella pertussis*, Fed. Proc. **27**: 268, 1968.
84. Castro de la Mata, R., Penna, M., and Aviado, D. M.: Reversal of Sympathomimetic Bronchodilation by Dichloroisoproterenol, J. Pharmacol. & Exper. Therap. **135**: 197, 1962.
85. Nagasaka, M., Bouckaert, J., De Schaepdryver, A. F., and Heymans, C.: Adrenergic Constriction in Isolated Guinea-Pig Lung Revealed by Nethalide, Arch. Internat. Pharmacodyn. **149**: 237, 1964.
86. Martinez, L., de Letona, J., Castro de la Mata, C., and Aviado, D. M.: Local and Reflex Effects of Bronchial Arterial Injection of Drugs, J. Pharmacol. & Exper. Therap. **133**: 295, 1961.
87. Aviado, D. M.: Pharmacological Approach to Treatment of Atopic Disorders, *in* Samter, M., editor: Immunological Diseases, Boston, 1965, Little, Brown & Company pp. 612-619.
88. Levy, B., and Alquist, R. P.: Adrenergic Drugs, *in* DiPalma, J. R., editor: Drill's Pharmacology in Medicine, New York, 1965, McGraw-Hill Book Company, Inc., p. 468.
89. Szakacs, J. E., and Cannon, A.: L-Norepinephrine Myocarditis, Am. J. Clin. Path. **30**: 425, 1958.
90. Mond, E., and Mack, I.: Cardiac Toxicity of Iproniazid (Marsilid): Report of Myocardial Injury in a Patient Receiving Levarterenol, Am. Heart J. **59**: 134, 1959.
91. Pogatsa, G., and Gabor, Gy.: Beitrage zum Mechanismus der Myokardschadigung durch Noradrenalin, Acta Secundi Conventus Medicinae Internae Hung. Cardiologia, Budapest, pp. 346-349, 1963.
92. Pugh, R. C. B., Pickering, G. W., and Blacket, R. B.: The Production of Vascular Lesions and Cardiac Hypertrophy by Infusions of Renin and Noradrenaline in the Rabbit, Clin. Sc. **11**: 241, 1952.
93. Samson, P. C.: Tissue Changes Following Continuous Intravenous Injection of Epinephrine Hydrochloride into Dogs, Arch. Path. **13**: 745, 1932.
94. Jellinek, H., Huttner, I., Kerenyi, T., Gabor, Gy., and Pogatsa, G.: Fibrinoid Necrosis of the Vascular Wall Induced by Noradrenaline, Acta morphol. **14**: 183, 1966.
95. Jasmin, G., and Bajusz, E.: Etude Pathogénique des Lésions Cardiaques, Rénales et Musculaires Provoquées Chez le Rat par la Méthoxamine et le Métaraminol, Rev. Canad. Biol. **23**: 67, 1964.
96. Mishkin, F., and Wagner, H. N., Jr.: Regional Abnormalities in Pulmonary Arterial Blood Flow During Acute Asthmatic Attacks, Radiology **88**: 142, 1967.
97. Lecks, H. I., Whitney, T., Wood, D., and Kravis, L. P.: Newer Concepts in the Occurrence of Segmental Atelectasis in Acute Bronchial Asthma and Status Asthmaticus in Children, J. Asthma Res. **4**: 65, 1966.
98. Koelle, G. B.: Neurohumoral Transmission and the Autonomic Nervous System, *in* Goodman, L. S., and Gilman, A., editors: The Pharmacological Basis of Therapeutics, New York, 1965, The Macmillan Company, pp. 399-440.
99. Kaiser, G. A., Ross, J., Jr., and Braunwald, E.: Alpha and Beta Adrenergic Receptor Mechanism in the Systemic Venous Bed, J. Pharmacol. & Exper. Therap. **144**: 156, 1964.
100. Haddy, F. J., Gordon, P., and Emanuel, D. A.: The Influence of Tone Upon Responses of Small and Large Vessels to Serotonin, Circulation Res. **7**: 123, 1959.

101. Helander, E., Lindell, S. E., Nilsson, K., and Westling, H.: Catabolism of C^{14} Labeled Histamine in Patients With Allergic Diseases, Acta allergol. **17:** 86, 1962.
102. Beall, G. N., and Van Arsdel, P. P., Jr.: Histamine Metabolism in Human Disease, J. Clin. Invest. **39:** 676, 1960.
103. Dowell, R. C., Kerr, J. W., and Park, V. A.: The Metabolism of C^{14} Histamine in Subjects with Bronchial Asthma, J. ALLERGY **38:** 290, 1967.
104. Munoz, J., and Bergman, R. K.: Activity of Histamine Sensitizing Factor (HSF) from *B. pertussis*, Fed. Proc. **24:** 444, 1965.
105. Bergman, R. K., and Munoz, J.: Circulatory Collapse in Anaphylaxis and Histamine Toxicity in Mice, J. Immunol. **95:** 1, 1965.
106. Pieroni, R. E., and Levine, L.: Properties of the Immunogenic and Sensitizing Activities of *Bordetella pertussis* in Mice, J. ALLERGY **39:** 25, 1967.
107. Collier, H. O. J., James, G. W. L., and Piper, P. J.: Intensification by Adrenalectomy or by Beta-Adrenergic Blockade of the Bronchoconstrictor Action of Bradykinin in Guinea Pig, J. Physiol. **180:** 13, 1965.
108. Ouellette, J. J., and Reed, C. E.: The Effect of Partial Beta Adrenergic Blockade on the Bronchial Response of Hay Fever Subjects to Ragweed Aerosol, J. ALLERGY **39:** 160, 1967.
109. McNeill, R. S.: Effect of a Beta-Adrenergic Blocking Agent, Propranolol on Asthmatics, Lancet **2:** 1101, 1964.
110. Zaid, G., and Beall, G. N.: Bronchial Response to Beta-Adrenergic Blockade, New England J. Med. **275:** 580, 1966.
111. McNeill, R. S., and Ingram, C. G.: Effect of Propranolol on Ventilatory Function, Am. J. Cardiol. **18:** 473, 1966.
112. Besterman, E. M. M.: Discussion to the Paper of McNeill, R. S., and Ingram, C. G.: Effect of Propranolol on Ventilatory Function, Am. J. Cardiol. **18:** 473, 1966.
113. Besterman, E. M. M., and Friedlander, D. H.: Clinical Experiences with Propranolol, Postgrad. M. J. **41:** 526, 1965.
114. Goodman, L. S., and Nickerson, M.: Clinical Applications of Adrenergic Blockade: A Critical Appraisal, M. Clin. North America **34:** 379, 1950.
115. Curry, J. J., Fuchs, J. E., and Leard, S. E.: The Effect of Dihydroergocornine on the Pulmonary Response to Metacholine and Histamine in Subjects with Bronchial Asthma, J. Clin. Invest. **29:** 439, 1950.
116. Pieroni, R. E., Broderick, E. J., and Levine, L.: The Soluble Protective Antigen and Histamine-Sensitizing Factor of *Bordetella pertussis*, J. Immunol. **95:** 643, 1965.
117. Munoz, J., and Hestekin, B. M.: Antigens of *Bordetella pertussis*. III. The Protective Antigen, Proc. Soc. Exper. Biol. & Med. **112:** 799, 1963.
118. Van Hermert, P., Van Wezel, A. L., and Cohen, H. H.: Preparation of Soluble Pertussis Vaccine, Nature **203:** 774, 1964.
119. Joo, I., and Pusztai, Z.: Interconnection Between the Protective Antigen and the Histamine-Sensitizing Factor of *Bordetella pertussis*, Nature **188:** 331, 1960.
120. Niwa, M., Hiramatsu, T., Kawasaki, N., and Kuwajima, Y.: On the Relationship Between Histamine Sensitizing Factor and Mouse Protective Antigen, Jap. J. M. Sc. & Biol. **18:** 175, 1965.
121. Kind, L. S.: Effects of Heat on the Sensitizing and Shocking Properties of *Hemophilius pertussis*, J. Immunol. **77:** 115, 1956.
122. Munoz, J. J.: Symposium on Relationship of Structure of Micro-organisms to Their Immunological Properties. I. Immunological and Other Biological Activities of *Bordetella pertussis* Antigens, Bact. Rev. **27:** 325, 1963.
123. Pieroni, R. E., and Levine, L.: Adjuvant Principle of Pertussis Vaccine in Mouse, Nature **211:** 1419, 1966.
124. Pieroni, R. E., and Levine, L.: Further Studies on the Adjuvant Principle of Pertussis Vaccine for the Mouse, Nature **213:** 1015, 1967.
125. Parfentjev, I. A., and Manuelidis, E. E.: Hemopoietic Response in Mice Injected with Pertussis Vaccine, Fed. Proc. **15:** 607, 1956.
126. Fichtelius, K. E., and Hassler, O.: Influence of Pertussis Vaccine on the Lymphocyte Production in Adrenalectomized Rats, Acta. path. et microbiol. scandinav. **42:** 189, 1958.
127. Morse, S. I.: Studies on the lymphocytosis Induced in Mice by *Bordetella pertussis*, J. Exper. Med. **121:** 49, 1965.
128. Paget, G. E.: Carcinogenic Action of Pronethalol, Brit. M. J., **2:** 1266, 1963.
129. Alcock, S. J., and Bond, P. A.: Observations on the Toxicity of "Alderlin" (Pronethalol) in Laboratory Animals, Proc. of the European Soc. for the Study of Drug Toxicity **4:** 30, 1964.
130. Ehrich, W. E.: Lymphoid Tissues: Their Morphology and Role in the Immune Re-

sponse, *in* Samter, M., editor: Immunological Diseases, Boston, 1965, Little, Brown & Company, pp. 251-277.
131. Benner, M. H., Enta, T., Lockey, S., Jr., Makino, S., and Reed, C. E.: The Immunosuppressive Effect of Epinephrine and the Adjuvant Effect of Beta-Adrenergic Blockade, J. ALLERGY **41**: 110, 1968.
132. Perkins, E. H., Robinson, M. A., and Makinodan, T.: Agglutinin Response, Function of Cell Number, J. Immunol. **86**: 533, 1961.
133. Makinodan, T., and Albright, J. F.: Proliferative and Differentiative Manifestations of Cellular Immune Potential, Progr. Allergy **10**: 1, 1966.
134. Leduc, E. H., Coons, A. H., and Connoly, J. M.: Studies on Antibody Production. II. The Primary and Secondary Responses in the Popliteal Lymph Node of the Rabbit, J. Exper. Med. **102**: 61, 1955.
135. Wissler, R. W., Fitch, F. W., LaVia, M. F., and Gunderson, C. H.: The Cellular Basis for Antibody Formation, J. Cell. & Comp. Physiol. **50**: 265, 1957.
136. Nossal, G. J. V.: Antibody Production by Single Cells. II. The Difference Between Primary and Secondary Response, Brit. J. Exper. Path. **40**: 118, 1959.
137. Schayer, R. W., and Ganley, O. H.: Relationship of Increased Histidine Decarboxylase Activity to *Bordetella pertussis* Vaccine Sensitization of Mice, J. ALLERGY **32**: 204, 1961.
138. Simke, J., Graeme, M. L., and Sigg, E. B.: Bradykinin Induced Bronchoconstriction in Guinea Pigs and Its Modification by Various Agents, Arch. internat. pharmacodyn. **165**: 291, 1967.
139. Szentivanyi, A., and Norwood, W.: Structural Requirements for Sensitization by Beta Adrenergic Blocking Agents to the Pharmacological Mediators of Antigen-Antibody Responses. To be published.
140. McGready, S., Conboy, K., and Townley, R.: The Effect of Beta-Adrenergic Blockade on Bronchial Sensitivity to Methacholine in Normal and Allergic Rhinitis Subjects, J. ALLERGY **41**: 108, 1968.
141. Bullough, W. S.: Hormones and Mitotic Activity, Vitamins & Hormones **13**: 261, 1955.
142. Bullough, W. S.: The Control of Mitotic Activity in Adult Mammalian Tissues, Biol. Rev. **37**: 307, 1962.
143. Bullough, W. S.: A Study of the Hormonal Relations of Epidermal Mitotic Activity in vitro, Exper. Cell. Res. **7**: 186, 1954.
144. Lettre, H.: Effect of B-Phenylethylamine on Fibroblasts In Vitro, Ztschr. Physiol. Chem. **271**: 200, 1941.
145. Bullough, W. S.: Stress and Epidermal Mitotic Activity. I. The Effects of the Adrenal Hormones, J. Endocrinol. **8**: 265, 1952.
146. Bullough, W. S., and Laurence, E. B.: The Energy Relations of Epidermal Mitotic Activity Adjacent to Small Wounds, Brit. J. Exper. Path. **38**, 273, 1957.
147. Bullough, W. S., and Laurence, E. B.: The Control of Mitotic Activity in Mouse Skin. Dermis and Hypodermis, Exper. Cell. Res. **21**: 394, 1960.
148. Bullough, W. S., and Laurence, E. B.: The Study of Mammalian Epidermal Mitosis In Vitro, Exper. Cell. Res. **24**: 289, 1961.
149. Belleau, B.: The Mechanism of Drug Action at Receptor Surfaces. Part I. Introduction. A General Interpretation of the Adrenergic Blocking Activity of B-Haloalkylamines, Canad. J. Biochem. & Physiol. **36**: 731, 1958.
150. Belleau, B., and Burba, J.: Occupancy of Adrenergic Receptors and Inhibition of Catechol O-Methyl-Transferase by Tropolones, J. Med. Pharm. Chem. **6**: 755, 1963.
151. Belleau, B., and Triggle, D. J.: Blockade of Adrenergic A-Receptors by a Carbonium Ion, J. Med. Pharm. Chem. **5**: 636, 1962.
152. Calabresi, P., and Welch, A. D.: Chemotherapy of Neoplastic Diseases, Ann. Rev. Med. **13**: 147, 1962.
153. Antopol, W.: The Production of the Shwartzman Phenomena by Means of Bacterial Extracts, J. Infect. Dis. **61**: 331, 1937.
154. Stetson, C. A., Jr.: Endotoxins and Bacterial Allergy, *in* Lawrence, H. S., editor: Cellular and Humoral Aspects of the Hypersensitive States, New York, 1959, Paul B. Hoeber, Inc., pp. 442-450.
155. Antopol, W.: The Use of Tumor Extracts in the Production of the Shwartzman Phenomenon, J. Infect. Dis. **61**: 334, 1937.
156. Antopol, W., and Glick, D.: Organs as a Source of Factors Capable of Eliciting the Shwartzman Phenomenon, Proc. Soc. Exper. Biol. & Med. **38**: 346, 1938.
157. Landy, M., and Shear, M. J.: Similarity of Host Responses Elicited by Polysaccharides of Animal and Plant Origin and by Bacterial Endotoxins, J. Exper. Med. **106**: 77, 1957.
158. Thomas, L.: Mechanisms Involved in Tissue Damage by the Endotoxins of Gram Negative Bacteria, *in* Lawrence, H. S., Editor: Cellular and Humoral Aspects of the Hypersensitive States, New York, 1959, Paul B. Hoeber, Inc., pp. 451-468.
159. Zweifach, B. W., Nagler, A. L., and Thomas, L.: The Role of Epinephrine in the Re-

actions Produced by the Endotoxins of Gram-Negative Bacteria. II. The Changes Produced by Endotoxin in the Vascular Reactivity to Epinephrine, in the Rat Mesoappendix and the Isolated, Perfused Rabbit Ear, J. Exper. Med. **104**: 881, 1956.
160. Zweifach, B. W.: Discussion to Reference 154, pp. 466-468.
161. Rall, D. P., and Kelly, M. G.: The Role of Vasoconstriction in the Local Shwartzman Reaction, J. Exper. Med. **105**: 643, 1957.
162. Zweifach, B. W.: Discussion to Part II., *in* Landy, M., and Braun, W., editors: Bacterial Endotoxins, New Brunswick, 1964, Rutgers University Press, pp. 146-150.
163. Palmerio, C., Ming, S. C., Frank, E., and Fine, J.: The Role of the Sympathetic Nervous System in the Generalized Shwartzman Reaction, J. Exper. Med. **115**: 609, 1962.
164. Brunson, J. G.: Relationships Between Endotoxin and Sympathomimetic Amines, *in* Landy, M., and Braun, W., editors: Bacterial Endotoxins, New Brunswick, 1964, Rutgers University Press, pp. 126-133.
165. Gerlach, W.: Studien über hyperergische Entzundung, Virchows Arch. path. Anat. **247**: 294, 1923.
166. Frohlich, A.: Ueber lokale gewebliche Anaphylaxie, Ztschr. Immunitätsforsch. **20**: 476, 1914.
167. Rossle, R.: Ueber die Merkmale der Entzundung in allergischen Organismus, Verhandl. deutsch. path. Gesellsch. **17**: 281, 1914.
168. Roulet, F.: Ueber die granulomartige allergische Entzundung, Verhandl. deutsch. path. Gesellsch. **26**: 189, 1931.
169. Klinge, F.: Die Eiweissuberempfindlichkeit (Gewebsanaphylaxie) der Gelenke, Beitr. path. Anat. **83**: 185, 1929.
170. Kallos, P., and Pagel, W.: Experimentelle Untersuchungen uber Asthma Bronchiale, Acta med. scandinav. **91**: 292, 1937.
171. Klemperer, P., Pollack, A. D., and Baehr, G.: Diffuse Collagen Disease, J. A. M. A. **119**: 331, 1942.
172 Gell, P. G. H.: Cytologic Events in Hypersensitivity Reactions, *in* Lawrence, H. S., editor: Cellular and Humoral Aspects of the Hypersensitive States, New York, 1959, Paul B. Hoeber, Inc., pp. 43-66.
173. Pagel, W.: Pathologie und Histologie der Allergischen Erscheinungen, Fortschr. Allergie-lehre. **1**: 98, 1939.
174. McMaster, P. D.: General and Local Vascular Reactions in Certain States of Hypersensitivity, *in* Lawrence, H. S., editor: Cellular and Humoral Aspects of the Hypersensitive States, New York, 1959, Paul B. Hoeber, Inc., pp. 319-353.
175. Bohrod, M. G.: Histology of Allergic and Related Lesions, Progr. Allergy **4**: 31, 1954.
176. Letterer, E.: Die Allergisch-hyperergische Entzundung, *in* Handbuch d. allgem. Pathologie, Bd. VII/1, hsg. von Buchner, F., Letterer, E., and Roulet, F., Berlin, 1956, Springer Verlag, u. die Morphologie der Immunopathischen Reaktion, ebenda, Bd. VII/2-1966.
177. Letterer, E.: Allgemeine Pathologie des Bindegewebes (unter Einschluss der Sogenannten Kollagenosen), Verhandl. deutsch. Gesellsch. inn. Med. 65. Kongr. Wiesbaden, 1959, Bergmann, Munchen, 1959.
178. Aviado, D. M., Winuck, A. L., and DeBeer, E. T.: Cardiovascular Effects of Sympathomimetic Bronchodilators, J. Pharmacol. & Exper. Therap. **122**: 406, 1958.
179. Ouellette, J. J., and Reed, C. E.: Increased Response of Asthmatic Subjects to Methacholine after Influenza Vaccine, J. ALLERGY **36**: 558, 1965.
180. Braunsteiner, H., and Dienstl, F.: Inhibition of Eosinophile Decrease Following Adrenalin Through Blockade of Adrenergic Beta Receptors, Klin. Wehnschr. **54**: 48, 1967.
181. Reed, C. E., Cohen, M., and Enta, T.: Comparison of the Effect of Epinephrine on Circulating Eosinophils of Normal and Asthmatic Subjects, J. ALLERGY **39**: 127, 1967.
182. Hechter, O.: Discussion to Reference 29, pp. 644-646.
183. Falliers, C. J.: Asthma and Cybernetics, J. ALLERGY **38**: 265, 1967.
184. Pearson, R. S. B.: Status Asthmaticus, *in* Jamar, C., editor: International Textbook of Allergy, Springfield, Ill., 1959, Charles C Thomas, Publisher, pp. 310-321.
185. Cookson, D. U., and Reed, C. E.: A Comparison of the Effects of Isoproterenol in the Normal and Asthmatic Subject, Am. Rev. Resp. Dis. **88**: 636, 1963.
186. Middleton, E., Jr., and Finke, S. R.: Metabolic Response to Epinephrine in Asthma, J. ALLERGY **39**: 103, 1967.
187. Inoue, S.: Effects of Epinephrine on Asthmatic Children, J. ALLERGY **40**: 337, 1967.
188. Lockey, S. D., Glennon, J. A., and Reed, C. E.: Comparison of Some Metabolic Responses in Normal and Asthmatic Subjects to Epinephrine and Glucagon, J. ALLERGY **40**: 349, 1967.
189. Herxheimer, H., and Kahle, G.: Der Einfluss von Adrenalin auf den Kreislauf, die Atmung und den Blutzucker von, Asthmatikern, Acta allergol. **12**: 269, 1957.
190. Kirkpatrick, C. H., and Keller, C.: Effects of Infusion of Epinephrine Into Patients With Respiratory Allergy and Chronic Bronchitis, Clin. Res. **14**: 438, 1966.

191. Tsuchiya, Y., and Bukantz, S. C.: Studies on Status Asthmaticus in Children. I. Capillary Blood pH and pCO_2 in Status Asthmaticus, J. ALLERGY **36**: 514, 1965.
192. Blumenthal, J. S., Brown, E. B., and Campbell, G. S.: Molar Sodium Lactate in Acute Epinephrine-Fast Asthmatic Patients, Ann. Allergy **14**: 506, 1956.
193. Blumenthal, J. S., Blumenthal, M. N., Brown, E. B., and Campbell, G. S.: Effect of Changes in Arterial pH on the Actions of Adrenalin in Acute Adrenalin-Fast Asthmatics, Dis. Chest **39**: 516, 1961.
194. Mithoefer, J. C., Runser, R. H., and Karetzky, M. S.: The Use of Sodium Bicarbonate in the Treatment of Acute Bronchial Asthma, New England J. Med. **272**: 1200, 1965.
195. Turiaf, J., Marland, P., Basset, G., and Georges, R.: Interêt de la Mesure des Gaz du Sang pour la Sécurité et l'Effcacite du Traitement de l'Etat de Mal Asthmatique Grave, XXXIIIe Congres Français de Medicine, Paris, 1961, Communication Masson & Cie.
196. Turiaf, J., Georges, R., Basset, G., and Marland, P.: Equilibre Acide-Base et Taux des Gaz du Sang dans l'Asthme, Rev. tuberc. **26**: 238, 1962.
197. Ramey, E. R., and Goldstein, M. S.: The Adrenal Cortex and the Sympathetic Nervous System, Physiol. Rev. **37**: 155, 1957.
198. Goldstein, M. S., and Ramey, E. R.: Non-Endocrine Aspects of Stress, Perspect. Biol. Med. **1**: 33, 1957.
199. Brodie, B. B., Davies, J. I., Hynie, S., Krishna, G., and Weiss, B.: Interrelationships of Cathecholamines With Other Endocrine Systems, Pharmacol. Rev. **18**: 273, 1966.
200. Bush, I. E.: Chemical and Biological Factors in the Activity of Adrenocortical Steroids, Pharmacol. Rev. **14**: 317, 1962.
201. Butcher, R. W., Jr., and Sutherland, E. W.: Enzymatic Inactivation of Adenosine-3′, 5′-Phosphate by Preparations from Heart, Pharmacologist **1**: 63, 1959.
202. Butcher, R. W., and Sutherland, E. W.: Adenosine 3′, 5′-Phosphate in Biological Materials I. Purification and Properties of Cyclic 3′, 5′-Nucleotide Phosphodiesterase and Use of This Enzyme to Characterize Adenosine 3′, 5′-Phosphate in Human Urine, J. Biol. Chem. **237**: 1244, 1962.
203. Meier, J., Lydtin, H., and Zollner, N.: Uber die Wirkung von adrenergen B-Rezeptorenblockern auf ventilatorische Funktionen bei obstruktiven Lungenkrankheiten, Deutsche. med. Wchnschr. **91**: 145, 1966.
204. Filipp, G., and Szentivanyi, A.: Zur Frage der Organlokalisation der allergischen Reaktion, Wien. klin. Wchnschr. **65**: 620, 1953.
205. Raskova, H., and Vanecek, J.: Pharmacology of Bacterial Toxins, Pharmacol. Rev. **16**: 1, 1964.
206. Munoz, J., and Bergman, R. K.: Histamine-Sensitizing Factors from Microbial Agents With Special Reference to *Bordetella pertussis*, Bact. Rev. **32**: 103, 1968.
207. Lecks, H. I., Wood, D. W., Baker, L., and Donsky, G.: Metabolic Response of Asthmatic Children to Epinephrine Infusion, J. ALLERGY **41**: 106, 1968.